Original Article

Chromosomal Patterns, Demographics, Clinical Features, and Karyotype-Phenotype Correlation in Patients with Turner Syndrome

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Abstract

Background: Turner Syndrome (TS) is caused by the complete or partial absence/abnormality of the second X chromosome in some or all cells.

The purpose of this study was to assess the correlation between clinical presentation and karyotype variations of X chromosome in TS.

Methods: In a retrospective case-series using medical records (2001-17) for our pediatric-endocrinology TS patients, additional data were collected using a questionnaire and detailed physical examination, including demographics, initial presentation, clinical characteristics at diagnosis, height, puberty stage, cardiovascular and renal malformations, uterus and ovary status, and hormonal profile. Three patient-groups of monosomy X (45,X) cases, 45,X/46,XX or 45,X/46,XY mosaicism cases, and cases with other aberrations of X chromosome were compared in this study.

Results: In 57 TS patients (Age range 6 months to 25 years (Mean 11.85±5.1 yrs.)), 3.5% were diagnosed in infancy because of lymphedema and congenital heart disease. Short stature was the initial presentation in 78.9%. On presentation, 94.7% were short. Other referrals included cases with primary amenorrhea (12%), delayed puberty (5.3%), leg edema (1.8%) and congenital heart disease (1.8%). Mean height standard deviation score was 3.7±1.8 SD below mean for age and sex. Overall, 50.9% of cases had all clinical features consistent with TS and 21.1% had no symptoms of TS other than short stature. Of 39 patients in pubertal age, 31.6% had degrees of breast maturity. Most of them had X structural abnormalities (40.3%). However, 33.3% had classic TS. Still, 5.3% had Y-chromosome material. Among three karyotype groups, clinical symptoms and phenotypes were not significantly different.

Conclusion: The study found no correlation between the clinical presentation and karyotype variations of TS.

Keywords: Amenorrhea, Chromosomes, Gonadal dysgenesis, Karyotype, Turner syndrome

Introduction

Turner Syndrome (TS) is caused by the complete or partial absence of the second X chromosome (monosomy) in some or all cells or presence of structurally abnormal X chromosome. TS presents with wide range of somatic features including characteristic facial features (webbed neck, low-set or maltreated ears, ptosis), short stature, premature ovarian failure, sexual infantilism, primary amenorrhea, congenital cardiac malformations, and skeletal abnormalities (1). Major phenotypic characteristics in TS are short stature and ovarian dysgenesis. Clinical features in TS may be highly varied (2). Haploinsufficiency of the X-linked genes that escape X inactivation is one of the key factors responsible for clinical phenotype of TS (3,4). Genes involved in the development and maintenance of the ovarian function are postulated to be on Xp and Xq (3,5). Previous studies have shown phenotype/karyotype correlations, so that patients with 45, X karyotype tend to have more severe form of disease and congenital defects than those having mosaic karyotypes with a normal cell line (45,X/46,XX or 45,X/46,XY) (6). With highly variable genetic background of the TS, different phenotypes can be expected (7). Despite this, karyotype variations have not reliably predicted the clinical presentation of individuals with TS (7).

In this study, an attempt was made to explore available data on karyotype and clinical profile and karyotype-phenotype correlation in TS patients.

Materials and Methods

This retrospective case-series was conducted on female Iranian patients diagnosed with TS proved by karyotyping in our outpatient pediatric-endocrinology center. Data collection was performed by reviewing the medical files, a questionnaire, and detailed physical examination. The main outcome measures were demographics and clinical characteristics at diagnosis, the main cause of referral to clinic, height, puberty stage, cardiovascular and renal malformations, uterus and ovary status, and hormonal profile. The patients were categorized into three groups based upon karyotype.

The Ethics and Research Committee of Hamadan University of Medical Sciences approved and funded the study (Study number: p/16/35/1/4644). All patients and their parents provided informed consents. Study participants were phenotypic female patients diagnosed with TS through cytogenetic analysis. Correlation between the karyotypes and clinical features was analyzed.

Data collection was performed by an experienced physician through reviewing the medical files recorded from 2001 to 2017. Additional required data were collected using a questionnaire and detailed physical examination.

Data were obtained on age of clinical presentation, age of diagnosis, presenting complaints, height Standard Deviation Score (SDS or z-score), blood pressure, clinical stigmata of TS, pubertal stage of breast and pubic hair development, sonographic appearances of the ovaries and uterus, echocardiogram findings, renal structural anomalies, and chromosomal analyses. Measurement of weight and height were done using SECA Beam scale (0.01 *kg*) and SECA measuring mat for height (0.1 *cm*) (Germany). Sexual maturation was assessed according to Tanner staging. Arterial blood pressure was measured using mercury sphygmomanometer with appropriate cuff size in two separate occasions. Hypertension was defined as over 95th percentile of blood pressure according to standardized table of age, gender and height. Dimensional echocardiography and electrocardiography were used to diagnose cardiac anomalies. Renal structural anomalies were diagnosed based on ultrasound examinations. Ultrasound examination of the uterus and the ovaries were performed in patients aged 12 years or older. Fasting blood glucose, thyroid function tests, renal function tests, lipid profile, and screening to rule out celiac disease using Anti TTG antibody were done in all patients at diagnosis. Serum FSH and LH measurements were done in all patients ≥10 years of age. FSH, LH, Thyroid Stimulating Hormone (TSH), and free T4 tests were done by electrochemiluminescence assays. Puberty was considered delayed if there were no secondary sexual characteristics by 13 years of age (8). Definitive TS diagnosis was done through chromosomal analysis. Standard chromosomal analyses of the cases were carried out using the basis of G-banding technique at high resolution. For each case, metaphase stages of 50-cell were examined from peripheral blood lymphocytes according to guidelines

from the International System for Human Cytogenetic Nomenclature (ISCN2005) (9). Diagnosis of TS or variants was considered by the presence of a 45,X cell line or mosaic forms of TS with 45,X/46,XX or additional cell lines with the Y chromosome (45,X/46,XY), structural abnormalities of the X like deletions of the short arm q or long arm p (Xp-, Xq- respectively), or duplication of the long arm to form isochromosome (isoXq) or ring (rX) (10).

Patients were categorized into three groups based on karyotype: cases with classic monosomy X (45,X), cases with XX or XY mosaicism, and those with other X chromosomal anomalies including structural aberrations of X chromosome. Clinical features of all groups were analyzed.

Patients who did not have all above mentioned criteria including data for blood pressure, TSH, pelvic sonography, and pubertal stage were excluded from the study.

Statistical analysis

SPSS version 16 (SPSS Inc., Chicago, USA) was used to analyze data. Descriptive data were presented as numbers, percentages, and means. Since quantitative variables were normally distributed, one-way ANOVA was used to compare the means among three groups, while chi-squared test was used to compare qualitative data between groups. Statistical significance was set as p-value <0.05.

Results

Medical records for 57 female patients with TS were reviewed (Mean age at diagnosis was 11.85±5.1 years, range of 6 months to 25 years). Of these, 9 (15.8%) had parental consanguinity. About 3.5% of the patients were diagnosed in infancy because of lymphedema and congenital heart disease. Diagnosis was on average 3 years delayed after the initial presentation of TS. Short stature was the initial manifestation in 45 (78.9%) cases. However, on presentation, 54 (94.7%) of them were clinically short. Mean height SDS (Standard deviation score or z score) was 3.7 ±1.8 SD below the mean for age and sex (range of -6.8 to +0), whereas 3 (5.3%) had a height curve above the 5th percentile in the normal female growth chart. Overall, 29 (50.9%) had all clinical features consistent with TS stature. Sixteen patients had one of the following features: 3 cases with ptosis (5.3%), 4 with web necked (7%), 4 with widely separated nipples (7%), 2 with pigmented nevi (3.5%), 2 with leg edema (3.5%), and 1 with nail dystrophy (1.8%). In 12 (21.1%) cases, no other symptoms of TS other than short stature was present.

Cardiac anomalies and congenital renal malformations were found in 15 (26.3%) and 4 (7%) cases, respectively. The most common cardiovascular malformations in these patients were bicuspid aortic valve in 8 (14%) and Coarctation Of the Aorta (COA) in 2 (3.5%). Horseshoe kidney was the main renal defect followed by duplex collecting system. Overall, 12 (21.1%) cases had overt hypothyroidism (TSH≥10 *mIU/L*). Clinical and laboratory characteristics of patients are reported in tables 1-3.

The most common karyotype was X structural abnormalities (40.3%) including 45X, 46XI observed in 10 (17.5%) cases. The classical monosomy (45X) was observed in 22 (33.3%) cases while 12 (21.1%) were diagnosed with 45,X/46,XX or 45,X/46,XY mosaicism (Table 2). Y-chromosome materials were seen in 3 (5.3%) patients.

Short stature was approximately universal in all patients regardless of karyotype abnormalities (p=0.57). The mean age at diagnosis and mean height were not different among three groups. Among the three groups with distinct karyotypic abnormalities, the phenotype was similar to the 45,X group. The classical monosomy group did not have more severe clinical features than those with other forms (Table 3). Our results showed that none of patients had impaired fasting glucose, or overt diabetes mellitus, dyslipidemia, or celiac disease marker at the time of diagnosis.

Discussion

This case-series studied association between karyotypes and clinical stigmata of patients with TS in selected patients from our setting. The TS patients mostly presented with X chromosome structural abnormalities (40.3%) and one third of cases had monosomy X chromosome. Patients showed a range of physical features of TS with different karyotypes where short stature was the most common feature (94.7%). Short stature was also the most common reason for seeking medical attention (76.4%) followed by delayed puberty.

Table 1. Detailed characteristics of 57 studied Turner syndrome patients

Characteristics	Number	Percent
Initial presentation:		
Short stature	45	78.9%
Amenorrhea	7	12.3%
Delayed puberty	3	5.3%
Edema	1	1.8%
Congenital heart disease	1	1.8%
Parental consanguinity	9	15.8%
[a]Height SD (*cm*)	-3.75 (-6.8-0)	
Full clinical stigmata of t urner syndrome	29	50.9%
Breast development		
Prepubertal age	18	31.6%
Pubertal age:	39	68.4%
SMR1	21	36.8%
SMR2	9	15.8%
SMR3	7	12.3%
SMR4	2	3.5%
SMR5	0	0%
Pubic hair development		
Prepubertal age	18	31.6%
Pubertal age:	39	68.4%
SMR1	5	8.7%
SMR2	22	38.6%
SMR3	10	17.5%
SMR4	2	3.5%
SMR5	0	0%
Congenital heart disease	15	26.3%
Bicuspid aortic valves	9	15.8%
COA	3	5.26%
AS (aortic stenosis)	1	1.8%
Bicuspid aortic valves + COA	1	1.8%
Bicuspid aortic valves + AS	1	1.8%
Congenital renal anomalies	4	7%
Mean blood pressure (*mmHg*):		
Diastole	6.3 (4-9)	
Systole	10.59 (6-16)	
Mean TSH *mIU/L*	7.84 (1-55)	
Abnormal TSH ≥4.5 *mIU/L*	24	42.1%
TSH ≥10 *mIU/L*	12	21 %
TSH between 4.5 - 9.99 *mIU/L*	12	21%
Mean FSH (*mIU/mL*)	81.91 (1-164.8)	
Mean LH (*IU/L*)	20.08 (0.18-55)	
Sonographic appearances of the ovaries (39 were at puberty age)		
Normal ovaries	8	14%
Streak gonad	17	29.8%
Absent	14	24.6%
Sonographic appearances of the uterus (39 were at puberty age)		
Normal uterus	10	17.5%
Small uterus	26	45.6%
Absent uterus	3	5.3%

[a] This variable means standard deviation (SD) relative to the mean height of the same age.

SMR: Sexual Maturity Rating; COA: Coarctation of the aorta; FSH: Follicle-stimulating hormone; LH: Luteinizing Hormone; TSH: Thyroid stimulating hormone.

Table 2. Distribution of patients with Turner syndrome in three main groups of karyotypes and their descriptive details (N =57)

Karyotype	Frequency	Percent	Valid Percent
Group 1: 45,X Mono-somy	22	33.3	33.3
Group 2: XX and XY Mosaicism	12	21.1	21.1
Group 3: X Structural Abnormalities	23	40.3	45.6
45XO	22	38.6	33.3
45XDEL/46XX	2	3.5	3.5
46XXMarker	2	3.5	3.5
45X/46XX	5	8.8	8.8
46XI	2	3.5	3.5
45X/46XMARK	2	3.5	3.5
45X/46XI	10	17.5	17.5
45X/46XY	2	3.5	3.5
46XDEL	5	8.7	8.7
45X/47XXX	4	7.0	7.0
46XX/46XY	1	1.8	1.8

Cytogenetic studies have indicated that SHOX haploinsufficiency (normally located in the pseudo-autosomal region of short arm of chromosome X) appears to be the main cause of short stature and skeletal abnormalities including short metacarpals, cubitus valgus, or Madelung deformity of patients with TS (8,11).

The mean age at diagnosis was 11.85±5.1 years which is consistent with other studies (12), although it is still higher than that observed in developed countries (13). Appropriate strategies are needed including raising parents' awareness of their short girls and enabling physicians and health care providers to refer suspected cases of TS for early diagnosis.

Although many girls with TS can be identified by their declining growth rates within the first years of life, the diagnosis often takes place later and underdiagnosis is common (1). The most important causes of delayed diagnosis include wide range of dysmorphic features,

Table 3. Comparison of characteristics among distinct chromosome groups (N = 57)

	45X Monosomy	X Chromosome Structural Abnormalities	XX and XY Mosaicism	p Value
Mean age at presentation (years)	10.1	13.3	11.9	0.18
Mean Height (*cm*)	119.8 (61-153)	125.9 (90.50-150.00)	126.33 (77.00-150)	0.529
SD Height (*cm*)	-3.62	-3.41	-4.01	0.398
Short stature as Initial presentation	17	10	19	0.335
Short stature in examination	17	11	26	0.256
Breast development of 39 patients in pubertal age				
SMR1	16	7	16	0.318
SMR2	1	3	5	
SMR3	1	1	5	
SMR4	1	1	0	
SMR5	0	0	0	
Pubarche SMR				
SMR1	9	3	11	0.145
SMR2	7	7	8	
SMR3	1	2	7	
SMR4	2	0	0	
SMR 5	0	0	0	
Congenital Heart Malformation				
Yes	8	3	4	0.132
No	11	9	22	
Renal Structural Anomalies				
Yes	1	0	3	0.405
No	18	12	23	
Systolic Hypertension	10.27 (6-14)	10.62 (8-14)	10.80 (6-16)	0.676
Sonographic Appearances of the Ovaries				
Normal	2	3	3	0.337
Small	8	2	7	
Absent	4	5	5	
Sonographic Appearances of the Uterus				
Normal	5	3	2	0.396
Small	9	6	11	
Absent	0	1	2	

SMR: Sexual Maturity Rating. One-way ANOVA was used to compare quantitative parameters among three groups, while chi-squared test was used to compare qualitative data between groups. SD: standard deviation. A p-value <0.05 was considered as statistically significant.

absence of characteristic stigmata in some cases, disregard for clinical examinations by physicians or lack of clinical expertise, and parents' neglect of short girls. The main reason for seeking medical advice is lack of pubertal development rather than short stature. However, early identification of TS allows a good chance for increasing growth velocity and improving the final adult's height by Growth Hormone (GH) therapy (14). Timely screening and management of possible co-existing illnesses in TS will also improve quality of life and may significantly reduce the morbidity and mortality of affected individuals. Considering the benefits of early detection, special emphasis should be placed on proper clinical examination and consideration of TS by physicians for any girl with unexplained short stature. This may help achieving ideal response to currently available therapies.

Although no significant difference was found between patients with 45,X and those with other variants of TS in terms of differences in phenotypic characteristics, Elleuch *et al* and Zheng *et al* reported that patients with 45,X completely differ in their phenotypical abnormalities (15,16).

Consistent with previous studies (17), about half of our patients (53.8%) did not show any signs of pubertal development, while others had at least some degrees of breast development. Previous investigations that focused on the gonadal functions in girls with mosaicism 45,X/47,XXX or 45,X/46,XX karyotypes have depicted an increased likelihood of undergoing spontaneous pubertal development and menarche in those girls (18). However, in our study, these associations were not clear.

Congenital heart malformations were detected in 12 (21%) cases, which was in agreement with the findings of other investigators (10). The most common cardiovascular malformations in TS patients were bicuspid aortic valve and aortic coarctation. However, no correlation was found between either karyotype and the type of congenital heart defects.

Renal structural anomalies identified through ultrasound were present in 7 (13.4%) of our study subjects, which was lower in comparison with previous reports (19). The low frequency of renal malformations was thought to be due to small number of studied patients or underdiagnosis while using ultrasound. In support of relevant literature (19), no association was found between prevalence of kidney malformation and specific types of karyotype. Since the congenital renal anomalies increase the risk of hypertension, urinary tract infections, and hydronephrosis (20), in line with previous studies, it is suggested that any patient with TS must receive a thorough clinical and radiologic evaluation including intravenous urography of urogenital tract at the time of diagnosis (18,19).

With respect to hypertension, 3.5% of our patients were diagnosed with high blood pressure. However, the prevalence of hypertension varied in previous studies from 7 to 17% (21). Hypertension can be present from childhood in patients with TS with involvement of various factors such as heart malformations, obesity, obstructive sleep apnea, metabolic syndrome, and hormone replacement therapy may cause increased blood pressure in individuals with TS (20). Since high blood pressure may increase the risk of aortic dissection, a periodic and regular blood pressure measurement is highly recommended.

As expected, plasma levels of gonadotropins, particularly FSH, were markedly elevated in most of our patients. Basically, TS results from either total/partial absence or structural aberrations of one of two X chromosomes. It is therefore possible that lack of related genes involved in the development and maintenance of the ovarian function results in premature ovarian failure and consequently, sexual infantilism, delayed puberty, primary amenorrhea, and infertility. Laboratory finding of this condition is hypergonadotropic hypogonadism (3). Although the genetic mechanisms contributing to the viability of oocytes and thus for normal ovarian function are still not determined, it seems that the complete chromosomal pairing is a prerequisite for the survival of the oocytes and the development of normal ovaries. It is unclear whether premature ovarian failure is caused by genes on X chromosome or other autosomal defects are involved. In this regard, Castronovo *et al* suggested that not only haploinsufficiency of X-linked genes, but also autosomal-linked mutations might be involved in ovarian phenotype of TS patients (22). However, further research is required to identify the phenotypic impact of possible autosomal-linked genes on ovarian function It is preferred to begin female sex hormone replacement therapy at a normal pubertal age with bone age of 12 for our patients.

In agreement with previous studies (23), the frequency of subclinical (TSH >4.5 *mIU/L*) and overt hypothyroidism (TSH>10 *mIU/L*) was significantly high in our study too. No association was observed between the incidence of thyroid problems and karyotype. A new meta-analysis revealed that autoimmune thyroid diseases occur in more than one-third of patients with TS (23). Untreated hypothyroidism may result in further growth failure and severe short stature in TS. Therefore, routine laboratory screening for hypothyroidism is recommended at diagnosis and annually thereafter in TS patients.

The structural alteration of the X chromosome was the dominant anomaly (40.3%) which is similar to the data reported by Carvalho *et al* (42%) (12). One third of cases had X chromosome monosomy. The

frequency of classic type of Turner syndrome (XO) in our study is similar to those presented in the studies by Wu *et al* (32.7%), Al Alwan *et al* (30.8%), and Kammoun *et al* (32%) (24-26). However, it is slightly different from the study results of Bharath *et al* (45.8%) (9).

Finally, although our patients presented a diverse spectrum of clinical findings and karyotype profile, our three karyotype groups did not differ in initial presentation, age at diagnosis, height, puberty stage, uterus and ovary status, renal ultrasound findings, hormonal profile, cardiovascular and urinary systems anomalies, and frequency of any specific feature. The number of dysmorphic features was not correlated with type of chromosome aberrations. However, in contrast, Liang *et al* (27) reported that the patients with 45,XO karyotype have more severe gonadal dysfunction than those with other karyotypes. Kammoun *et al* also established a correlation between chromosome profile and the clinical expression of TS (24). Since conventional chromosomal analyses do not allow identifying low levels of mosaicisms, it is not possible to make a definitive comment on the hypotheses of karyotype and phenotype correlation in TS.

In alignment with the current literature (28), cell line with Y chromosome has been detected in 5.3% of our patients. Nevertheless, due to using conventional karyotyping, some cells containing a Y chromosome might have lost. In view of the risk of developing gonadoblastoma, previous researchers have recommended that analysis by PCR should be carried out in all patients with TS in order to detect Y-chromosome-specific sequences, regardless of their karyotype (26). Given that the presence of Y chromosome or fragment may be associated with an increased risk of developing gonadoblastoma in patients with TS (29), laparoscopy was carried out and dysgenetic gonads were removed in all our three patients with Y chromosome.

One of the limitations of this study was its retrospective nature and records of clinical findings might have been incomplete. Moreover, some of the related problems including intellectual status, osteoporosis, inflammatory bowel disease, and hearing status were not thoroughly investigated. Also, MRI was not performed for diagnosis of COA or assessment of anti-thyroid peroxidase antibody levels. So, the prevalence of COA and auto-immune thyroid disease in this study is not clear. In addition, Y chromosome sequences were not checked in this research. If patients were classified into two groups namely "classic Turner syndrome (XO)" and "other abnormalities of X chromosomes", it could be quite possible to obtain different results. It is worth mentioning that it was a pilot study on a relatively small sample with TS, so larger studies with longer follow-up period up to adulthood may provide better opportunities to assess associated problems in TS patients.

Conclusion

In this study, no correlation between clinical features of TS and the type of chromosome aberrations was found. However, our patients had a wide range of chromosomal abnormalities. There was a considerable delay between initial presentation and the age of diagnosis in our medical setting. Bringing awareness to the parents with short girls helps them to seek medical care at earlier ages, which is clinically beneficial for the patients in terms of taking advantage of follow-ups and available therapies.

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Conflicting Interest

The authors declare that they have no competing interests.

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